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Catalytic asymmetric direct α-alkylation of amino esters by aldehydes *via* imine activation†

Biao Xu,‡[a] Li-Li Shi,‡[a] Yu-Zu Zhang,[a] Zhi-Jun Wu,[b] Li-Na Fu,[a] Chun-Qin Luo,[a] Lan-Xi Zhang,[a] Yun-Gui Peng[a] and Qi-Xiang Guo*[a]

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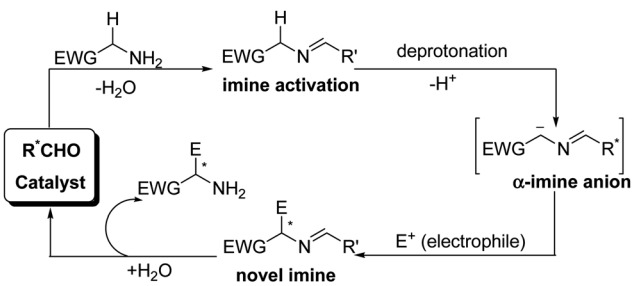
Two types of BINOL-related chiral aldehydes were used as organocatalysts for the direct α-functionalization of *N*-unprotected amino esters. The first chiral aldehyde catalysed α-alkylation of 2-aminomalonates with 3-indolylmethanols *via* imine activation was reported. Various tryptophan derivatives were produced in good yields and with high enantioselectivities. A reasonable mechanism was proposed and the core intermediates were identified by high resolution mass spectroscopy (HRMS).

The development of new approaches in asymmetric organocatalysis is an important and longstanding field.[1] During the last decade, diverse chiral organocatalysts, including enamine catalysts,[2] Brønsted acids[3] and bases,[4] phase-transfer catalysts,[5] carbenes[6] and ketones,[7] have been developed. Numerous excellent organocatalytic methodologies have been found to construct optically active natural and unnatural compounds. Despite these great achievements, current chiral organocatalysts have rarely been used in the direct asymmetric α-functionalization of *N*-unprotected amines, which is an important strategy for the preparation of chiral free amine compounds.[8] Enantioselective phase-transfer catalysis is an excellent strategy for the α-functionalization of free amines. However, it is an indirect method, as the reactant imines are prepared in advance and the free amine products are released by a further hydrolysis step.[5] The development of methodologies for the direct asymmetric α-functionalization of *N*-unprotected amines is thus highly desirable. It is known that the α-C–H bond of an amine can be activated by an aldehyde *via* the formation of an imine,[9,10] and this imine formation is reversible, which make the use of chiral aldehydes as catalysts for the direct α-activation of *N*-unprotected amines possible. However, chiral aldehydes have never been used as organocatalysts in this respect. Alternatively, combinations of chiral pyridoxal analogs and metal salts can be used as catalysts to activate the α-C–H bonds of amino acids *via* the formation of transamination intermediates,[11] and some chiral aldehydes have been used as tethering catalysts.[12] Due to the importance of the direct asymmetric α-functionalization of free amine compounds, we hypothesized the possibility of chiral aldehyde catalysed direct α-activation of *N*-unprotected active amines *via* imine activation (Scheme 1). Here we report our attempt to achieve this using an alkylation reaction as a model.

Chiral BINOL skeletons exhibit excellent asymmetric induction in organic transformations.[13] Inspired by the molecular structure of BINOL-derived Brønsted acid catalysts,[3a–c] we synthesized two types of chiral BINOL-related aldehydes **4** and **5** (Fig. 1). These chiral BINOL aldehydes have the characteristics necessary to serve as good organocatalyst candidates: (1) the catalytic sites are adjacent to the chiral axis centers; (2) the Ar group of **4** and the R group of **5** can be easily tuned, and (3) the hydroxyl groups of **5** are good hydrogen-bond donors and acceptors. We therefore chose these BINOL-related chiral aldehydes as organocatalysts in this work. As a continuation of our work towards the alkylation of carbonyl compounds with 3-indolylmethanols,[14] we chose the alkylation of 2-aminomalonates with 3-indolylmethanols as a model reaction. It is a challenging reaction, because the 2-potition of the indole has good nucleophilic ability, thus a Pictet–Spengler reaction may take place subsequently.[15] We speculated that this challenge



Scheme 1 Our hypothesised mechanism for chiral aldehyde catalysed α-functionalization of active amines *via* imine activation (EWG = Electron-Withdrawing Group).

[a]*School of Chemistry and Chemical Engineering, Southwest University, Beibei, Chongqing 400715, China. E-mail: qxguo@swu.edu.cn*

[b]*Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China*

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‡ These authors contributed equally to this work.

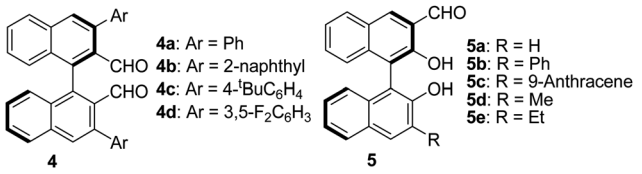
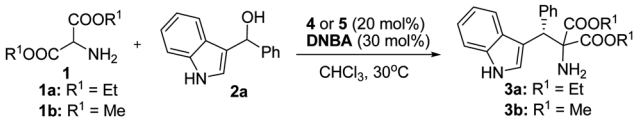


Fig. 1 Catalysts designed in this work.

could be overcome through adjusting the electronic and steric effects of the chiral aldehyde catalysts. This chiral aldehyde catalysed direct α-alkylation of 2-aminomalonates was used to validate our hypothesis shown in Scheme 1.

We first evaluated the catalytic and enantio-controlling of **4a** abilities in the direct alkylation of diethyl,2-aminomalonate **1a** with 3-indolylmethanol **2a**. The target product **3a** was obtained with 50% enantiomeric excess (ee), albeit in low yield (Table 1, entry 1). This reaction could not proceed in the absence of an aldehyde catalyst (Table 1, entry 2). Encouraged by these positive results, we screened the chiral aldehyde catalysts **4b–d** in this reaction (Table 1, entries 3–5). Disappointingly, although the enantioselectivity of **3a** was enhanced to 66% ee, the yields varied from 32% to 42%. The chiral aldehydes **5** were then introduced into the reaction. We hoped that the Brønsted acid site of **5** could form a hydrogen bond with the vinylogous imino intermediate derived from **2a**, increasing the stereo-controlling ability. When the chiral aldehyde **5a** was used as the catalyst, a good yield (66%) and high enantioselectivity (71% ee) were obtained (Table 1, entry 6). Various aryl groups were then introduced at the 3′-position of **5**. The chiral aldehyde **5b**, which has a phenyl group at the 3′-position, had the best stereo-controlling ability (81% ee; Table 1, entry 7). When diethyl 2-aminomalonate (**1a**) was replaced by the dimethyl derivative **1b**, the product **3b** was obtained with 82% ee (Table 1, entry 9). The enantioselectivity of **3b** increased to 84% when the reaction was carried out at 20 °C and the yield also increased slightly (Table 1, entry 10). Further optimization of the reaction conditions was then carried out by screening the solvents and acid additives (see the ESI†). Unfortunately, no better results were obtained. We then replaced the aryl group at the 3′-position in **5** with an alkyl (Table 1, entries 11–12). We found that catalyst **5d** was the best choice for this reaction in terms of yield (64%) and enantioselectivity (85% ee) (Table 1, entry 11). A cleaner reaction occurred when it was performed at lower temperature: the enantioselectivity increased to 86% (Table 1, entry 13). When we used 50 mol% of DNBA as the additive, the desired product **3b** was obtained with high enantioselectivity, but the yield decreased to 72% (Table 1, entry 14). The catalyst loading is very important for the yield. For example, when the catalyst loading was reduced, the yields were greatly reduced (Table 1, entries 15 and 16). The optimal reaction conditions were thus determined. Generally, the reaction was carried out in $CHCl_3$, promoted by 20 mol% of chiral aldehyde catalyst **5d**, and 30 mol% of DNBA at 20 °C.

Table 1 Optimization of reaction conditions (DNBA = 3,5-dinitrobenzoic acid)[a]

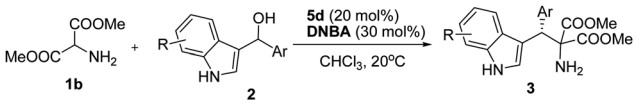


Entry	Cat.	1	Time (h)	Yield (%)[b]	ee (%)[c]
1	**4a**	**1a**	24	24	50
2[d]	—	**1a**	12	0	—
3	**4b**	**1a**	30	37	55
4	**4c**	**1a**	40	42	64
5	**4d**	**1a**	30	32	66
6	**5a**	**1a**	4	66	71
7	**5b**	**1a**	6	57	81
8	**5c**	**1a**	5	61	77
9	**5b**	**1b**	4	57	82
10	**5b**	**1b**	4	65	84[e]
11	**5d**	**1b**	6	64	85
12	**5e**	**1b**	6	60	84[e]
13	**5d**	**1b**	6	77	86[e]
14	**5d**	**1b**	6	72	87[e,f]
15	**5d**	**1b**	9	68	86[e,g]
16	**5d**	**1b**	12	55	85[e,h]

[a] Entries 1–4: **1** (0.2 mmol), **2a** (0.1 mmol), **4** or **5** (0.02 mmol), $CHCl_3$ (1 mL), 30 °C; 5–15: **1** (0.4 mmol), **2a** (0.2 mmol), **4** or **5** (0.04 mmol), $CHCl_3$ (2 mL), 30 °C. [b] Isolated yield. [c] Determined by HPLC. [d] No catalyst added. [e] At 20 °C. [f] Using 50 mol% DNBA. [g] Using 15 mol% **5d**. [h] Using 10 mol% **5d**.

With the optimal reaction conditions confirmed, we then explored the substrate scope. First, various substituents were introduced at the 2-position of the phenyl group of 3-indolylmethanols (Table 2, entries 2–6). We found that electron-withdrawing substituents decreased the reaction rate slightly (Table 2, entries 2–5). In particular, when 2-NO_2-phenyl-substituted **2** reacted with **1b**, the desired product **3f** was obtained in 49% yield after 5 days (Table 2, entry 5). Satisfactorily, the enantioselectivities of products **3c–3g** remained high (82–96% ee). The effects of substituents at other positions of the phenyl group were then tested. When either electron-withdrawing or electron-donating groups were introduced at the 3- or 4-position, the target products were obtained in moderate to high yields and with high enantioselectivities (Table 2, entries 7–12). Naphthyl-substituted 3-indolylmethanols were also examined in this reaction. The bulky 1-naphthyl group gave better enantioselectivity than 2-naphthyl did, but the yield was lower (Table 2, entry 13 *vs* 14). Subsequently, the substrate scope was examined with respect to the substituents on the indole ring. 3-Indolylmethanols bearing an electron-withdrawing group at the 5-position of the indole were good partners in this reaction. For example, the 5-Br- and 5-Cl-indole-substituted **2** reacted with **1b** efficiently, giving the products **3p** and **3q** in high yields and with good enantioselectivities (Table 2, entries 15–16). The 6-F-indole-substituted acceptor produced the target compound **3r** in moderate yield and with excellent enantioselectivity (Table 2, entry 17). Furthermore, 7-Me-indole-substituted 3-indolylmethanols yielded the corresponding products in moderate yields, and the enantioselectivities varied from 92% to 98% ee (Table 2, entries 18–20). The absolute

Table 2 Substrate scope[a]



Entry	3	Ar	R	Time (h)	Yield (%)[b]	ee (%)[c]
1	**3b**	Ph	H	6	77	86
2	**3c**	2-ClC_6H_4	H	48	68	92
3	**3d**	2-BrC_6H_4	H	24	64	96
4	**3e**	2-FC_6H_4	H	24	62	91
5	**3f**	2-$NO_2C_6H_4$	H	120	49	95
6	**3g**	2-$MeOC_6H_4$	H	7	59	82
7	**3h**	3-FC_6H_4	H	5	88	87
8	**3i**	3-MeC_6H_4	H	18	42	84
9	**3j**	3-$MeOC_6H_4$	H	6	77	87
10	**3k**	4-MeC_6H_4	H	7	53	77
11	**3l**	4-BrC_6H_4	H	13	76	87
12	**3m**	4-$CF_3C_6H_4$	H	24	76	88
13	**3n**	1-Naphthyl	H	20	67	89
14	**3o**	2-Naphthyl	H	6	88	80
15	**3p**	1-Naphthyl	5-Br	10	86	82
16	**3q**	1-Naphthyl	5-Cl	10	84	79
17	**3r**	1-Naphthyl	6 F	21	49	94
18	**3s**	1-Naphthyl	7-Me	21	33	92
19	**3t**	2-BrC_6H_4	7-Me	41	43	98[d]
20	**3u**	2-ClC_6H_4	7-Me	15	67[e]	95[d]

[a] **1** (0.4 mmol), **2** (0.2 mmol), **5d** (0.04 mmol), DNBA (0.06 mmol), $CHCl_3$ (2 mL), 20 °C. [b] Isolated yield. [c] Determined by HPLC. [d] At 40 °C. [e] Approximate 46% HPLC purity.

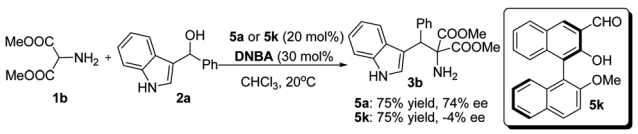
configuration of **3c** (*R*) was established by X-ray single-crystal analysis.[16] The stereochemistries of other products were assigned by analogy with those of **3c** (see the ESI†).

The possible mechanism of this chiral-aldehyde-catalyzed alkylation was then studied. It is well known that azomethine ylide dipoles are formed from aldehydes and dialkyl 2-aminomalonates.[9] We therefore think that the first step in our alkylation reaction is the formation of an azomethine ylide dipole **I** from catalyst **5d** and dimethyl 2-aminomalonate (**1b**). DNBA would promote the formation of vinylogous imine **2a′**.[14] The key issue in this mechanism is whether a hydrogen bond, similar to previously reported models,[17] is formed between the Brønsted acid site of **5d** and the vinylogous imino intermediate **2a′**. In order to clarify this, a control experiment was conducted. The catalyst **5k** was prepared by methylation of the 2′-OH chiral aldehyde **5a**. We found that the stereo-controlling abilities of **5k** decreased greatly (Scheme 2). We speculated that the lack of hydrogen-bond interaction between catalyst **5k** and active intermediate **2a′** is the most probable reason for this great decrease in enantioselectivity (see the ESI†). Based on these experimental results, we proposed the reaction mechanism shown in Fig. 2. First, the chiral aldehyde **5d** reacts with dimethyl 2-aminomalonate (**1b**) to form the azomethine ylide dipole **I**. Then the hydrogen of 2′-OH complexes with the nitrogen atom of vinylogous imino intermediate **2a′**, and then forms the transition state **TS I**. The azomethine ylide dipole **I** attacks the active intermediate **2a′** at the *si*- face and produces the imine **II**. Imine **II** produces the product **3b** and regenerates catalyst **5d** by hydrolysis or is converted to azomethine ylide dipole **I** by amine exchange with dimethyl 2-aminomalonate (**1b**).

In order to study our proposed reaction mechanism, we monitored the reaction process by HRMS (see the ESI†). In the positive-ion mode, we observed MS peaks of the key intermediates **2a′** (**2a′** + H^+: m/z = 206.0974), **I** (**I** + H^+: m/z = 458.1611) and **II** (**II** + H^+: m/z = 663.2514) after the reaction had proceeded for 5 minutes. After 30 minutes, the MS peak of product **3b** (**3b** + H^+: m/z = 353.1501) was detected. In the negative-ion mode, the key intermediates **I** (**I** − H^+: m/z = 456.1460) and **II** (**II** − H^+: m/z = 661.2343) were also detected. This evidence indicates that the reaction mechanism we proposed is reasonable. We found the catalyst **5d** could be observed initially in the negative-ion mode (**5d** - H^+: m/z = 327.1035), however, the intensity of the corresponding MS peak weakens gradually as the reaction progresses and becomes undetectable after 30 min. This observation suggests that catalyst **5d** may not be regenerated through a hydrolysis step, but rather that the intermediate **II** is converted to **I** preferentially by amine exchange.

The alkylation products were readily converted to tetrahydro-β-carbolines by Pictet–Spengler reactions[18] without loss of stereochemistries. For example, the β-aryl-substituted tryptophan derivative **3c** efficiently reacted with formaldehyde and cyclohexanone, affording the corresponding products **6a** and **6b**, with excellent enantioselectivities (Scheme 3).

In conclusion, chiral aldehydes have been successfully used as organocatalysts for the direct α-functionalization of *N*-unprotected amino esters. We described the first chiral aldehyde catalysed α-alkylation of 2-aminomalonates with



Scheme 2 Control experiment.

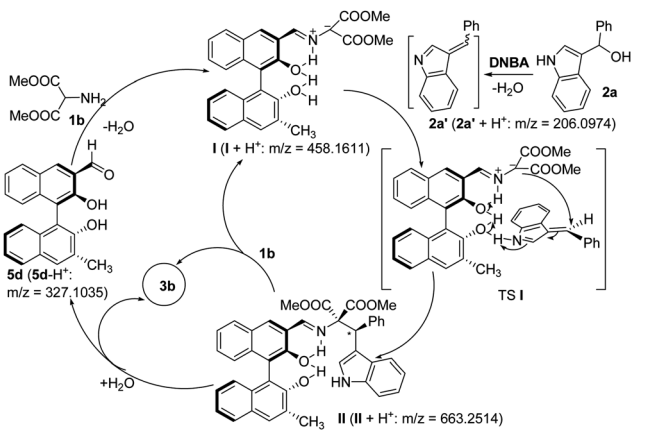
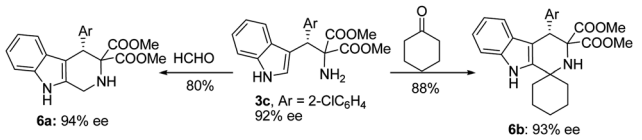


Fig. 2 Proposed catalytic cycle and rationale for stereoinduction.



Scheme 3 The synthesis of chiral tetrahydro-β-carbolines.

3-indolylmethanols. *N*-unprotected tryptophan derivatives were obtained in yields up to 88% and with 98% ee, and could be readily converted into tetrahydro-β-carbolines without loss of enantioselectivities. A reasonable reaction mechanism was proposed and the core intermediates were identified by HRMS. The catalysts and activation model revealed in this work will supplement current knowledge in organocatalysis.

Acknowledgements

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16 CCDC 965738 (3c) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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